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REGIOSPECIFIC ACYLATION REACTIONS OF IMIDAZO[1,5-a]PYRIDINE

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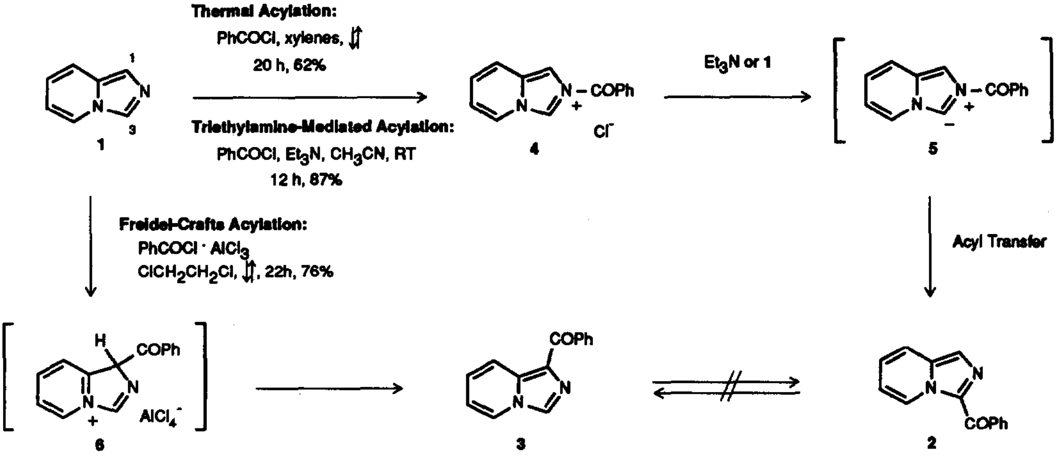
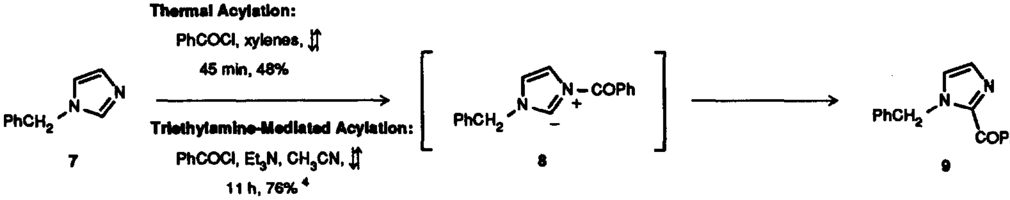
Imidazo[1,5-a]pyridine (**1**) *displays dual reactivity through two condition-dependent reaction pathways. Regiospecific acylation occurs with benzoyl chloride at the 1-position under Friedel-Crafts conditions to afford 3 or at the 3-position* <u>via</u> *a postulated, stabilized ylid 5 under thermal or triethylamine-mediated acylation conditions to give 2.*

The electrophilic substitution chemistry of imidazo[1,5-a]pyridine (**1**) has been reported (e.g. nitration, acylation, and Vilsmeier formylations[1]). These substitution reactions occur predominately at the 1-position, and reaction at the 3-position takes place when the 1-position is blocked. We have found that the site of acylation on **1** with benzoyl chloride can be controlled depending on the reaction conditions. In this paper, we propose reaction mechanisms which account for these regiospecific benzoylations.



The thermal acylation of imidazo[1,5-a]pyridine (**1**)[2] with benzoyl chloride in refluxing xylenes in the absence of Lewis acid resulted in reaction at the 3-position to give **2**, while Friedel-Crafts conditions gave the 1-benzoyl derivative **3**. These reactions were completely regiospecific as judged by TLC comparisons of the crude reaction mixtures. Additionally, when either **2** or **3** was subjected to reaction conditions under which the other regioisomer was formed, no interconversion occurred. This result suggests that these two processes through independent pathways lead to the reaction products **2** or **3**. A reasonable mechanism for the formation of the 3-benzoyl derivative **2** was not obvious initially. Although Friedel-Crafts acylation at the 1- or 3-position would produce σ-complexes of similar stability, the 1-position is the site of higher electron density than the 3-position; therefore, acylation is preferred at the 1-position.[3] This difference in site electron density was confirmed by the ^{13}C NMR spectrum of **1**. The chemical shift of the C-1 carbon was shielded by 9 ppm compared to that of the C-3 carbon.

Imidazoles have been proposed to acylate through an ylid species **8** to give the 2-acylimidazole **9**.[4] When the acylation reaction was run with **1** under literature conditions,[4] acylation occurred at the 3-position exclusively. Thus, treatment of **1** with triethylamine in acetonitrile followed by the addition of benzoyl chloride gave the 3-benzoyl derivative **2** in 87% yield. We propose that the thermal acylation reaction occurs by the same mechanism as the triethylamine-mediated acylation, i.e. through the ylid **5**. Further evidence for this conclusion was obtained by reacting 1-benzylimidazole under the thermal acylation reaction conditions. We found that analogous to **1**, 1-benzylimidazole yields the 2-benzoylimidazole **9**. The Friedel-Crafts acylation of 1-methylimidazole with the benzoyl chloride-aluminum chloride complex gave no reaction. Presumably 1-methylimidazole complexes with aluminum chloride preferentially and this complex is resistant to acylation.[5]



In the proposed reaction mechanism pathway outlined above, under the thermal acylation conditions, some equilibrium must exist for the formation of the ylid **5** by deprotonation of the acyl-quaternary compound **4**. The electron-deficient positively-charged heterocycle stabilizes the anion at the 3-position of the ylid. The reaction rate is slow in this case since **1** is a poor base and the reaction does require a higher reaction temperature. As a consequence of triethylamine being a much stronger base than **1**, pKa=11.0 and 5.54[6] respectively, the triethylamine-mediated acylation occurs at a lower temperature. The acyl transfer is most likely to occur intermolecularly. The acyl-quaternary compound **4** is a reactive acylating species and on formation the ylid **5** would react rapidly with **4**. An intramolecular acyl transfer would necessarily pass through a high energy species to yield product.

We have discovered that seemingly related reactions conditions afford exclusive acylation at the 1- or 3-position of imidazo[1,5-a]pyridine **1**. Imidazo[1,5-a]pyridine **1** was shown to exhibit similar reactivity as 1-benzylimidazole to afford acylation at the 3-position through a formal 1,2-acyl transfer via a postulated nitrogen ylid intermediate **5**. Unlike imidazoles, **1** undergoes Friedel-Crafts acylation to give the 1-benzoyl derivative **3**.

Footnotes and References:

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